Treatment of Postprandial Hypotension with a Somatostatin Analogue (SMS 201-995)

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A somatostatin analogue, compound SMS 201-995, was used to treat postprandial hypotension in a patient with autonomic neuropathy. Prior to treatment, the patient's mean blood pressure decreased 50 to 80 mm Hg after each meal, resulting in frequent loss of consciousness. Subcutaneous administration of low doses of compound SMS 201-995 (12 to 16 μg) prevented the postprandial hypotension. The therapeutic benefits of SMS 201-995 dissipated after a few hours, however, which made it necessary to administer the drug with each meal. No adverse effects of this agent were noted over a nine-month treatment period. Compound SMS 201-995 provided safe and effective therapy for postprandial hypotension.

Postprandial hypotension has been described in patients with parkinsonism [1] and autonomic neuropathy [2]. Blood pressure may decrease to dangerous levels in these conditions and patients may become confused or lose consciousness. We have recently observed that intravenous administration of somatostatin temporarily prevented postprandial hypotension in a patient with severe autonomic neuropathy [3]. We now report the results of treating this patient with the long-acting somatostatin analogue SMS 201-995 [4]. We found that SMS 201-995 provided safe and effective therapy for this patient's postprandial hypotension over a nine-month treatment period.

CASE REPORT

The patient was a 70-year-old white male with chronic alcoholism, autonomic neuropathy, hypoaldosteronism, esophageal stricture, and recurrent gastritis. He became hypotensive and frequently lost consciousness either after standing or eating a meal. Physical examination revealed a supine blood pressure of 150/70 mm Hg and an upright blood pressure of 65/30 mm Hg. The heart rate was 60 beats per minute and was unaffected by posture. Liver function test results and fasting plasma glucose levels were normal, and his serum potassium level was elevated (5.2 to 5.6 meq/dl). Addison's disease was excluded by the corticotropin stimulation test [3]. Nerve conduction velocity studies confirmed the presence of a sensory polyneuropathy. Autonomic neuropathy was confirmed by vasomotor reflex tests, which revealed that the heart rate did not vary appropriately in response to deep breathing or Valsalva's maneuver [5]. The supine-to-standing plasma norepinephrine increment was markedly attenuated (10 pg/ml).

MATERIALS AND METHODS

All studies were performed with the patient in bed after an overnight fast. All medicines except multi-vitamins and antacids were discontinued 72 hours before each experiment. The patient received a diet containing at least 120 meq

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Sandostatin (octreotide) is a registered trademark of Sandoz Pharmaceuticals Corporation, East Hanover, New Jersey. Sandostatin is also known as SMS 201-995, SMS, and somatostatin analogue.

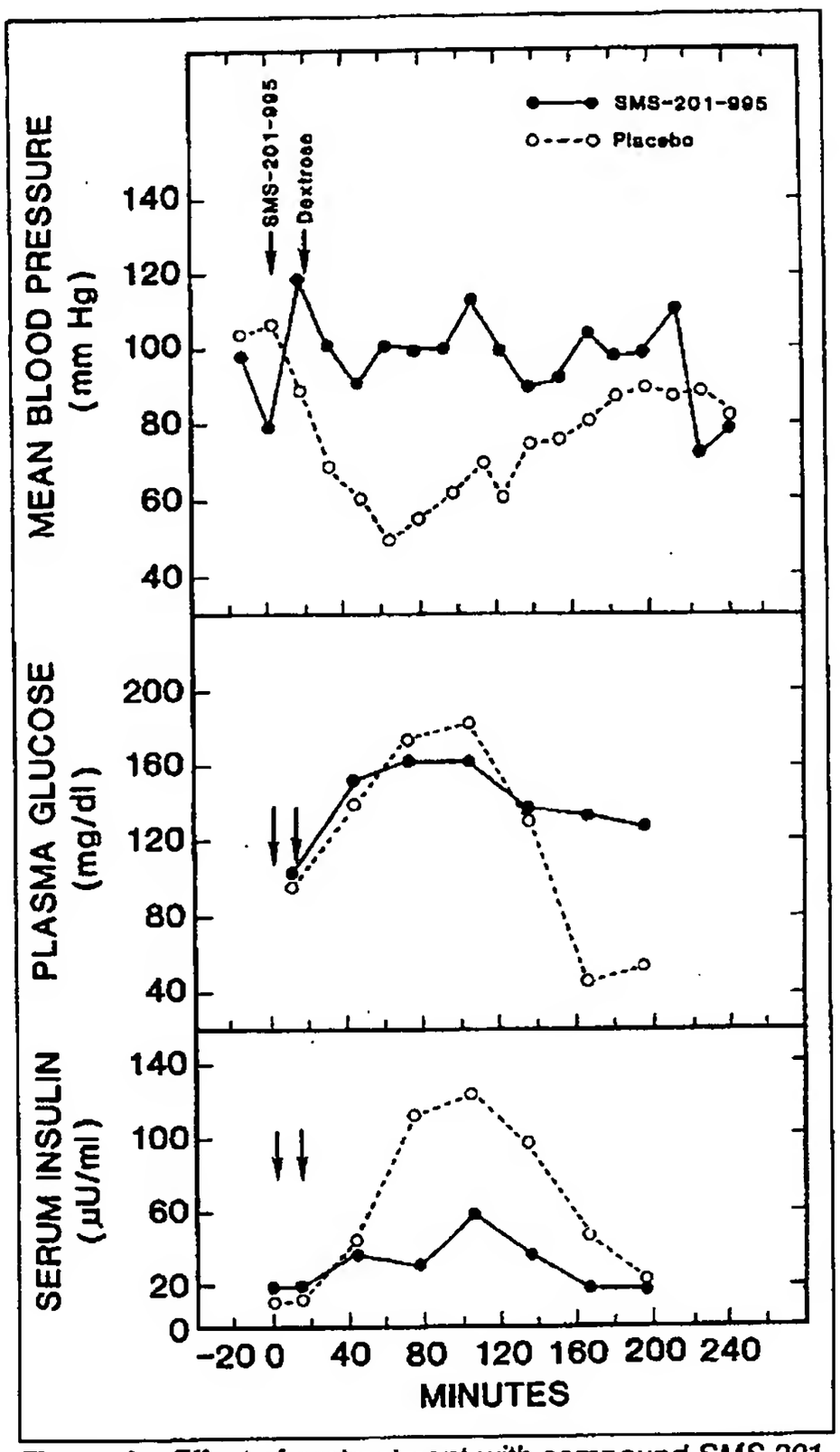

Figure 1. Effect of pretreatment with compound SMS 201-995 on postprandial blood pressure, plasma glucose, and serum insulin levels. Compound SMS 201-995 12.5 μg or a placebo was injected subcutaneously 15 minutes prior to giving 100 g of dextrose orally over 10 minutes. Blood samples were collected from an indwelling line for the determination of plasma glucose and serum insulin values. The head of the patient's bed was elevated 45 degrees throughout the study.

of sodium per day, and no more than 60 meq of potassium per day. The experimental nature of SMS 201-995 therapy was explained to the patient and his informed consent was obtained. The studies were approved by the Institutional Review Board of Temple University Hospital.

Mean blood pressure was measured with a Datascope Acutorr I (Paramus, New Jersey). Compound SMS 201-995 was provided by Sandoz Pharmaceuticals (East Hanover, New Jersey). Serum insulin concentration was measured by radioimmunoassay [6] and plasma glucose level was determined with a Beckman Glucose Analyzer. Plasma catecholamine levels were measured by a radioenzymatic method [7]. The plasma concentration of SMS 201-995 was measured by radioimmunoassay [4].

RESULTS

Effect of a Single Dose of SMS 201-995 on the Blood Pressure, Plasma Glucose Level, and Serum Insulin Response to a Dextrose Challenge. The ingestion of 100 g of dextrose caused a profound decrease in blood pressure that lasted for 2 to 4 hours, and was frequently associated with a loss of consciousness. The pulse rate was fixed at 56 to 60 beats per minute during the postprandial period. Subcutaneous administration of 12.5 μg of compound SMS 201-995 15 minutes prior to dextrose ingestion completely prevented postprandial hypotension (**Figure 1**). This beneficial effect disappeared after about three to four hours. Larger doses of SMS 201-995 (50 to 70 μg) similarly prevented postprandial hypotension but offered no advantage over 12.5 μg; neither administration of 50 μg nor 70 μg of SMS 201-995 in the morning (7:45 to 8:00 A.M.) prevented the hypotension that occurred after lunch (given four hours after breakfast). Insulin secretion was partially inhibited following administration of 12.5 μg of SMS 201-995, but hyperglycemia did not ensue (Figure 1); a 50-μg dose of the drug completely suppressed insulin secretion for three hours and resulted in hyperglycemia (a two-hour postprandial plasma glucose concentration of 200 to 220 mg/dl).

Effect of SMS 201-995 on the Blood Pressure Response to a Mixed Meal. The hemodynamic responses to mixed meals were similar to those following dextrose ingestion. Administration of a very small dose of SMS 201-995 (4 μg) with each meal attenuated hypotension following breakfast and prevented hypotension following lunch (**Figure 2**). Larger doses (12 to 16 μg) of the drug completely prevented hypotension following breakfast as well as that following lunch and supper (**Table I**).

Plasma Concentration of SMS 201-995 Following Its Subcutaneous Administration. The peak plasma concentration of SMS 201-995 (1.9 ng/ml) occurred at 90 to 120 minutes following 50-μg subcutaneous administration (**Table II**). Although the plasma half-life of SMS 201-995 could not be calculated from our data, it was evident that the drug remained in the circulation of our patient longer than would have been predicted from previous estimates of its plasma half-life, 100 to 110 minutes [4].

Long-Term Therapy with SMS 201-995. The patient has received 6 to 16 μg of compound SMS 201-995 with each meal for nine months, and his supine blood pressure has been effectively stabilized. Prior to therapy, the patient lost consciousness several times each week; during the nine months of therapy with SMS 201-995, he has lost consciousness only twice. No adverse effects have devel-

TABLE I Effect of Compound SMS 201-995 on Postprandial Blood Pressure

Treatment	Maximal Decrease in Mean Blood Pressure (mm Hg)
Placebo	55
SMS 201-995	
4 μg	26
8 μg	28
12 μg	4
16 μg	1

The patient was administered various doses of SMS 201-995 at the beginning of a standardized 500-kcal breakfast, and supine mean blood pressure was monitored at 15-minute intervals for the next three hours. The maximal decrease in mean blood pressure was calculated by subtracting the lowest postprandial blood pressure from the average of two baseline readings.

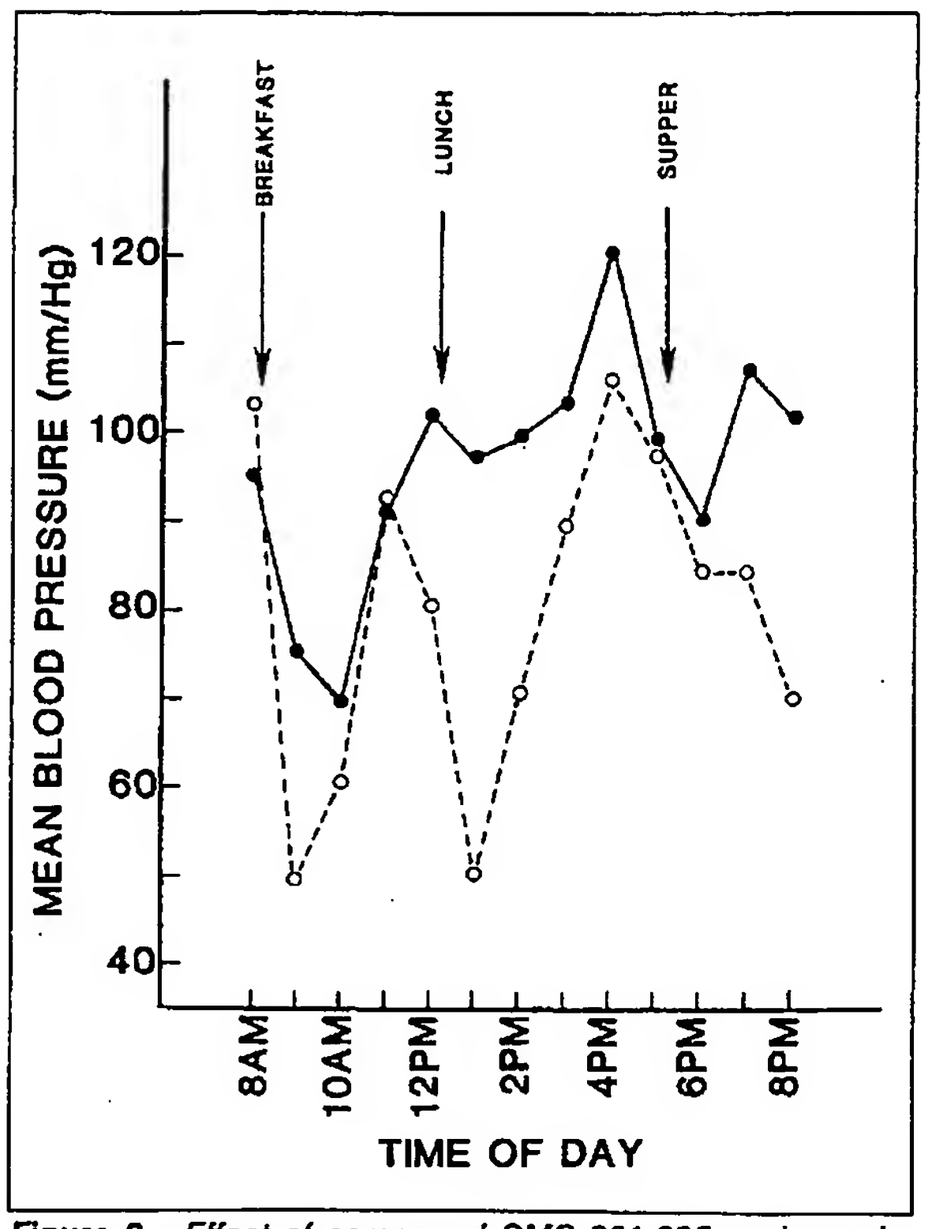

*Figure 2. Effect of compound SMS 201-995 on hemodynamic response to mixed meals. The patient was administered compound SMS 201-995 (4 μg) (**solid circles**) or a placebo (**open circles**) at the beginning of breakfast, lunch, and supper. The patient was supine for at least 5 minutes before each treatment was given twice; each data point represents the average reading from two separate days.*

oped. Hyperglycemia has not been observed in either the fasting or postprandial period. Hemoglobin A_{1C} increased from 5.8 to 6.8 percent (normal range, 5.1 to 7.8) during the first six months of therapy with the drug.

COMMENTS

These data demonstrate that a somatostatin analogue, SMS 201-995, stabilized blood pressure in a patient with postprandial hypotension. This study was prompted by the observation that a large dose (500 μg) of intravenous somatostatin temporarily prevented postprandial hypotension in this patient [3]. We now report that this same effect can be achieved with much smaller doses (12 to 16 μg) of a long-acting somatostatin analogue, and that long-term subcutaneous administration of this agent is clinically beneficial.

The physiologic basis for this therapeutic effect is unclear. Perhaps nutrients, upon contacting the gastrointestinal mucosa, stimulate the release of a vasoactive gastrointestinal peptide, which causes hypotension when compensatory sympathetic reflexes are inadequate. Vasoactive peptides, for example, have been implicated in the hypotensive crises that have been associated with the carcinoid syndrome, which can be reversed by treatment with SMS 201-995 [8]. Attempts to identify a vasoactive gut peptide in our patient have been unsuccessful thus far [3]. Alternatively, the beneficial effects of SMS 201-995 may result from a direct vasoconstrictor effect of the agent. Although no hemodynamic effects of SMS 201-995 have been observed in normal subjects [9] or patients with insulin-dependent diabetes mellitus [10], a slight pressor effect of large doses of this agent (100 to 200 μg) has recently been observed in patients with alcoholic cirrhosis

TABLE II Plasma Concentration of SMS 201-995 and Glucose and Serum Insulin Following an Injection of SMS 201-995

Plasma SMS 201-995 (ng/ml)	0	1:45	1.25	1.9	1.9	1.7	1.7
Mean blood pressure (mm Hg)	110	115	125	123	136	110	114
Plasma glucose (mg/dl)	93	116	127	176	207	185	176
Serum insulin (μU/ml)	10	2.5	2.5	3	4	10	13
Time (minutes)	0	30	60	90	120	150	180

Compound SMS 201-995 (50 μg) was injected subcutaneously at time zero, 8:30 A.M., at which time the patient was administered 100 g of dextrose orally. Blood was collected from an indwelling line at the indicated time intervals.

[11]. It is well known that patients with autonomic neuropathy may exhibit enhanced sensitivity to the pressor effects of a variety of drugs, including norepinephrine [12], tyramine [13], and arginine vasopressin [14].

In summary, the somatostatin analogue compound SMS 201-995 prevented postprandial hypotension in a patient with autonomic neuropathy over a nine-month treatment period. This agent may represent a new therapeutic option for patients with postprandial hypotension.

ACKNOWLEDGMENT

We thank Sandoz Pharmaceuticals for providing compound SMS 201-995.

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Discussion

Dr. G.W. Geelhoed: Do you think the somatostatin analogue could be used to treat dumping or the post-gastrectomy syndromes?

Dr. Robert D. Hoeldtke: As you are aware, there are a variety of post-gastrectomy syndromes. Those forms of dumping that are linked to rapid carbohydrate absorption might respond to SMS 201-995. I am unaware of any studies in this regard.

Dr. Aaron I. Vinik: One of the problems in managing patients with autonomic dysfunction is nocturnal supine hypertension. Might this not be aggravated by the treatment you recommend?

Dr. Hoeldtke: As with any pharmacologic therapy for orthostatic hypotension, supine hypertension cannot be totally avoided. We advise our patient not to lie down for the first three hours following the administration of SMS 201-995. To avoid nocturnal supine hypertension, we use a smaller dose of this agent with supper (4 to 6 μg) than with breakfast (12 to 16 μg).

Dr. Basil I. Hirschowitz: There are two possible mechanisms that you didn't discuss. One is the renin-angiotensin system. The second is a direct effect on the smooth muscle of the vessels. Have you considered these possibilities?

Dr. Hoeldtke: Somatostatin may suppress aldosterone responses to angiotensin II, an effect that is probably unrelated to the pressor effect of somatostatin we have observed (Clin Endocrinol 1985; 21: 279–284). We are unaware of studies on the effect of somatostatin on vascular smooth muscle.

Dr. Hirschowitz: Has SMS 201-995 been studied in patients with hypertension? Is it possible that the drug is dangerous in this group of patients?

Dr. Hoeldtke: The somatostatin analogue has no effect on blood pressure in normal persons, and I suspect it has little or no pressor effect in most patients with hypertension. In patients with supine hypertension secondary to autonomic dysfunction, SMS 201-995 might exhibit a significant pressor effect.

Dr. Thomas M. O'Dorisio: We initiated, on a compassionate basis, a trial of SMS 201-995 in a patient with a metastatic pheochromocytoma. Even a large dose of this

drug (200 μg, three times per day) had no effect on the blood pressure of this patient. There was certainly no evidence of a hypertensive effect of this agent.

Dr. Ariel Barkan: We have been using SMS 201-995 in patients with acromegaly, some of whom have hypertension. The somatostatin analogue tends to lower the blood pressure in these patients.

Dr. William E. Clutter: Have you examined the plasma norepinephrine response to oral glucose or meals in your patients? If so, does somatostatin or its analogue alter it?

Dr. Hoeldtke: That is an interesting question; we are in the process of performing those studies.

Dr. Hagop H. Mekhjian: Have you considered that SMS 201-995 may cause a redistribution of blood flow from the splanchnic to the peripheral circulation?

Dr. Hoeldtke: Yes. I suspect this is correct, which is the probable explanation of the pronounced pressor effect of SMS 201-995 during the postprandial period.

Dr. Mekhjian: Do you have any information on the secretion of somatostatin in these patients?

Dr. Hoeldtke: We have not studied that particular question. Dr. Vinik and his colleagues have observed that patients with non-insulin-dependent diabetes mellitus, some of whom had autonomic dysfunction, do not secrete somatostatin normally in response to a mixed meal or insulin hypoglycemia (J Clin Endocrinol Metab 1981; 52: 330–337).

Dr. M. Sue O'Dorisio: One possibility, particularly in diabetic neuropathy, might be a change in the biosynthesis or processing of the various molecular forms of somatostatin in degenerating neurons. This could be tested with selective antibodies in the radioimmunoassay, or by fractionating the somatostatin isolated from these patients using high-pressure liquid chromatography.

Dr. Jerome M. Feldman: Did treatment with SMS 201-995 have any beneficial effects on any other aspects of the autonomic neuropathy, such as impotence, sweating, or pain?

Dr. Hoeldtke: These are interesting questions, but we did not explore these possibilities.